

Brand Name: Eliquis®

Generic Name: apixaban

Manufacturer: Bristol-Myers Squibb Co.^{1,3}

Drug Class: Anticoagulant, Factor Xa inhibitor^{1,2,3,4}

Uses:

Labeled Uses^{1,2,3,4}: Stroke prophylaxis and systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation.^{1,2,3,4}

Unlabeled Uses^{2,4}: To reduce the risk of recurrent DVT and/or PE (in patients completing 6-12 months of standard anticoagulation for venous thromboembolism).² Postoperative DVT prophylaxis for arthroplasty of the knee.⁴ Postoperative DVT prophylaxis for total hip replacement.⁴

Mechanism of Action:^{1,2,3,4}

Apixaban is a reversible and selective factor Xa inhibitor, which does not require antithrombin III for antithrombotic activity.^{1,2,3,4} Apixaban inhibits both free and clot bound factor Xa, as well as inhibiting prothrombinase activity.^{1,2,3,4} Apixaban decreases thrombin generation and the development of a thrombus through the inhibition of factor Xa.^{1,2,3,4} Apixaban indirectly inhibits platelet aggregation through the inhibition of thrombin via the inhibition of factor Xa.^{1,2,3,4}

Pharmacokinetics^{1,2,3,4}:

Absorption:

T _{max}	3-4 hours ^{1,2,3,4}
V _d	21 L ^{1,2,3,4}
t _{1/2}	IV: ~5 hours; PO: ~12 hours ^{1,3,4} 2.5 mg dose (repeated oral administration): ~8 hours; 5 mg single dose: ~15 hours ²
Clearance	(not reported) ^{1,2,3,4}
Protein binding	87% (extant to albumin not reported) ^{1,2,3,4}
Bioavailability	50% ^{1,2,3,4}

Metabolism: Apixaban is primarily metabolized by CYP3A4 and to a lesser extent by CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2J2.^{1,2,3,4} O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation.¹ Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.³ Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.^{1,2,3}

Elimination: Apixaban is eliminated in both the urine and the feces.^{1,2,3,4} About 27% is excreted in the urine mostly unchanged.^{1,2,3,4} Approximately 25% is excreted in the feces as metabolites.^{2,3} Biliary and direct intestinal excretion contribute to fecal elimination.^{1,3,4}

Efficacy:

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.

Study Design: Multicenter, randomized, double-blind, double-dummy, parallel-group design study.

Description of Study: In this study, 18,206 patients with atrial fibrillation or flutter, and at least 1 additional risk factor for stroke, were randomized to receive either apixaban or warfarin. The study included patients with a history of warfarin, or other vitamin K antagonist use, and those with no prior history of use. After the titration phase, patients were monitored monthly for INR control, and every 3 months for assessment of clinical outcomes and adverse events. Guidance was provided to transition patients to open-label warfarin at the end of the study while still maintaining concealment of the treatment assignments and ensuring appropriate anticoagulation. *Outcome Measures:* The primary efficacy outcome was stroke, ischemic or hemorrhagic, or systemic embolism. The key secondary efficacy outcome was death from any cause. The primary safety outcome was major bleeding. *Results:* The primary outcome of stroke or systemic embolism occurred in 212 patients in the apixaban group (1.27%/year) as compared to 265 patients in the warfarin group (1.60%/year); $P < 0.001$ for noninferiority and $P = 0.01$ for superiority. The rate of death from any cause was lower in the apixaban group (3.52%/year) than in the warfarin group (3.94%/year) with $P = 0.047$. Major bleeding occurred in 327 patients in the apixaban group (2.13%/year), as compared with 462 patients in the warfarin group (3.09%/year) with $P < 0.001$.

Limitations: This study was funded by Bristol-Myers Squibb and Pfizer. Many of the authors were affiliated with or employed by Bristol-Myers Squibb, which introduces a potential for bias. In noninferiority trials such as this one, it is usually recommended that a per protocol analysis as well as an intention-to-treat analysis be performed. This trial did not include a per protocol analysis. In this study, the time in therapeutic range for warfarin (65%) was higher than other agents that have been compared to warfarin. However, the time in therapeutic range may be even higher for patients who have their warfarin managed by anticoagulation clinics.

Conclusion: This study shows that apixaban is superior to warfarin in preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation or flutter and at least one additional risk factor for stroke. This study also showed that apixaban resulted in both a statistically and clinically significant lower rate of major and clinically relevant nonmajor bleeding events compared to warfarin. Further studies are needed to determine

appropriate doses in those with severe renal impairment, creatinine clearance < 25mLs/min, and those with hepatic impairment.

Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med. 2011;365(23):2167-77.

Study Design: Multicenter, randomized, double-blind, double-dummy, parallel-group design study.

Description of Study: Male and female patients, 40 years of age or older, were considered for participation in the study if they were hospitalized for congestive heart failure, acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease and had an expected hospital stay of at least 3 days. Except for patients with congestive heart failure or acute respiratory failure, eligible patients had to have at least one of the following additional risk factors: age > 75 years, previous documented venous thromboembolism (VTE) or a history of VTE for which they received anticoagulation for at least 6 weeks, cancer, body-mass index of 30 or more, receipt of estrogenic hormone therapy, or chronic heart failure or respiratory failure. All patients had to be moderately or severely restricted in their mobility as well. 6,528 patients were randomized to receive either apixaban 2.5mg by mouth twice daily for 30 days and enoxaparin placebo once daily for a minimum of 6 days or enoxaparin 40mg subcutaneously once daily during their hospital stay for a minimum of 6 days and apixaban placebo twice daily. All compression ultrasound examinations were recorded for submission to an independent central adjudication committee whose members were unaware of the treatment assignments. *Outcome Measures:* The primary efficacy outcome was a composite during the 30-day treatment period of death related to VTE, fatal or nonfatal pulmonary embolism, symptomatic deep-vein thrombosis (DVT), or asymptomatic proximal-leg DVT as detected with the use of systematic bilateral compression ultrasonography. A key secondary efficacy outcome was the composite of total VTE and death related to VTE occurring from the time of randomization to the time the blinded parenteral therapy was discontinued. The main safety outcomes included major bleeding, clinically relevant nonmajor bleeding, and all bleeding reported by investigators. Myocardial infarction (MI), stroke, thrombocytopenia, and death from any cause were also safety outcomes. *Results:* The primary outcome of total VTE or VTE-related death during treatment period occurred in 60 patients in the apixaban group (2.71%) as compared to 70 patients in the enoxaparin group (3.06%); P= 0.44. The key secondary outcome of total VTE or VTE-related death during parenteral-treatment period occurred in 43 patients in the apixaban group (1.73%) as compared to 40 patients in the enoxaparin group (1.61%). Major bleeding events during the 30-day treatment period occurred in 15 patients in the apixaban group (0.47%) as compared to 6 patients in the enoxaparin group (0.19%); P= 0.04. Major plus clinically relevant nonmajor bleeding occurred in 85 patients in the apixaban group (2.67%) as compared to 67 patients in the enoxaparin group (2.08%); P= 0.12. A total of 246 bleeding events were reported in the apixaban group (7.73%) as compared to 219 in the enoxaparin group (6.81%); P= 0.18.

There was no significant difference in the rates of MI, stroke, thrombocytopenia, or death from any cause between the two groups.

Limitations: This study was funded by Bristol-Myers Squibb and Pfizer. Many of the authors were affiliated with or employed by Bristol-Myers Squibb, which introduces a potential for bias. This study was underpowered due to fact that a follow-up ultrasound was only performed on 64% of the study patients. This reduced the statistical power of the study making it difficult to draw any definitive conclusions from this study.

Conclusion: This study shows that some medically ill patients may remain at risk of developing a VTE long after their discharge from the hospital. Before we can determine who needs to be on long term prophylaxis, we first need to identify who is at risk. A well designed study that is accurately powered is needed to determine if apixaban could be a therapeutic option in these patients. Based on the results from this study apixaban does not result in a statistically significant reduction in VTE in medically ill patients when compared to enoxaparin, and apixaban has a higher incidence of bleeding events in medically ill patients compared to enoxaparin. Therefore, apixaban should not be recommended as a first line option for thromboprophylaxis in medically ill patients at this time.

Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. J Thromb Haemost. 2007;5(12):2368-75.

Study Design: Multicenter, randomized, double-blind, double-dummy, eight-arm, parallel-group Phase II trial. The warfarin arm was open label while the enoxaparin and apixaban arms were double-blind, double-dummy.

Description of Study: A total of 1,238 patients, aged 18-90 years, were randomly assigned to one of the following eight treatment groups: oral warfarin; s.c. enoxaparin (30 mg q12h); or one of six doses of oral apixaban (5, 10 or 20 mg q.d. or 2.5, 5 or 10 mg b.i.d.). Patients were screened daily while in hospital for suspected symptomatic DVT or PE, surgical or other bleeding, and other adverse events (AEs). Following discharge, patients were to call the study unit should any of these outcome events or AEs occur. Patients were followed clinically until a final visit, 30 days after the last dose of study medication (day 42). *Outcome Measures:* The primary outcome measure was a composite of asymptomatic and symptomatic DVT, symptomatic non-fatal PE, and death from any cause. The primary safety outcome was major bleeding. *Results:* The primary efficacy outcome occurred in 2 patients (1.8%) in the apixaban 2.5mg b.i.d. group, 2 patients (2.1%) in the apixaban 5mg q.d. group, 0 patients in the apixaban 5mg b.i.d. group, 2 patients (1.9%) in the apixaban 10mg q.d. group, 3 patients (2.7%) in the apixaban 10mg b.i.d. group, 2 patients (1.8%) in the apixaban 20mg q.d. group, 5 patients (4.6%) in the enoxaparin 30mg b.i.d. group, and 2 patients (1.8%) in the warfarin group. The primary safety outcome of major bleeding occurred in 0 patients in the apixaban 2.5mg b.i.d.

group, 4 patients (2.6%) in the apixaban 5mg q.d. group, 4 patients (2.6%) in the apixaban 5mg b.i.d. group, 1 patient (0.6%) in the apixaban 10mg q.d. group, 4 patients (2.6%) in the apixaban 10mg b.i.d. group, 5 patients (3.3%) in the apixaban 20mg q.d. group, 0 patients in the enoxaparin 30mg b.i.d. group, and 0 patients in the warfarin group.

Limitations: Several of the authors are consultants for Bristol-Myers Squibb and one of the authors is an employee of Bristol-Myers Squibb. This introduces a potential bias in the study. This study had a small number of patients in each treatment group making it difficult to extrapolate the results to the entire population and increasing the possibility for Type 2 error. The warfarin treatment group was open label introducing a potential for bias. Additionally the time in therapeutic range for warfarin was not reported, which may have significantly impacted the results of this study.

Conclusion: This study suggests that, when administered at doses of 2.5 mg b.i.d. started 12–24 h after completing knee replacement surgery; apixaban exhibits a benefit–risk profile comparable with the current standards of care with enoxaparin and warfarin. Doses higher than 2.5mg b.i.d. are associated with higher rates of bleeding than enoxaparin and warfarin. Additionally phase III trials with larger sample sizes are needed to confirm the results of this study before apixaban should be recommended for thromboprophylaxis in patients following total knee replacement.

Contraindications^{1,2,3,4}:

Active pathological bleeding: Apixaban use increases the risk of bleeding and may cause serious and potentially fatal bleeding.^{1,2,3,4} Concomitant use of drugs affecting hemostasis (i.e. nonsteroidal anti-inflammatories(NSAIDs), selective serotonin reuptake inhibitors(SSRIs), serotonin norepinephrine reuptake inhibitors(SNRIs), antiplatelets, thrombolytic agents, and other anticoagulants) increases the risk of bleeding.^{1,2,3,4} Patients should be educated on the signs and symptoms of bleeding and instructed to report them immediately or go to an emergency room.^{1,2,3,4}

Severe hypersensitivity to apixaban (i.e. anaphylactic reaction): Use in patients with a severe hypersensitivity reaction to apixaban or any component of the formulation is contraindicated.^{1,2,4}

Precautions^{1,2,3,4}:

Abrupt Discontinuation: Discontinuing apixaban puts patients at an increased risk for thrombotic events.^{1,2,3,4} If apixaban must be discontinued for reasons other than bleeding, strongly consider the use of another anticoagulant to prevent stroke from occurring.^{1,2,3,4}

Prosthetic Heart Valves: Use in patients with prosthetic heart valves has not been studied; use in this population is not recommended.^{1,2,3,4}

Surgery: Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures that have a moderate to high risk of unacceptable or clinically significant bleeding.^{1,2,3} Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where bleeding would not be in a critical location and easily controlled.^{1,2,3} Apixaban should be reinitiated when hemostasis has been achieved unless oral therapy cannot be administered, in which case parenteral anticoagulation should be considered.^{1,2,3}

Neuraxial Anesthesia: Spinal or epidural hematomas, including subsequent paralysis, may occur with neuraxial anesthesia (epidural or spinal anesthesia) or spinal puncture in patients who are anticoagulated.² Patients are at a higher risk if they are concurrently taking other drugs that affect hemostasis (i.e. SSRIs, SNRIs, NSAIDs, platelet inhibitors, or other anticoagulants), have a history of traumatic or repeated epidural or spinal punctures, or a history of spinal deformity or surgery.²

Adverse Effects^{1,2,3,4}:

> 10%

- Bleeding: (5% to 12%)⁴

1% to 10%

- Clinically-Relevant Non-Major Bleeding: (2% to 4%)²
- Nausea: (3%)²
- Anemia: (3%)²
- Major Bleeding: (\leq 2%)²
- Bruising: (1%)²
- Postprocedural Hemorrhage: (1%)²
- GGT Increased: (1%)²
- Transaminases Increased: (1%)²

< 1%

- Hypersensitivity Reactions: ($<$ 1%)^{2,3,4}
- Syncope: ($<$ 1%)^{1,2,3}
- Gastrointestinal Bleeding (upper GI, lower GI and rectal bleeding): (0.83%/year)^{1,3,4}
- Intracranial Bleeding: (0.33%/year)^{1,3,4}
- Intraocular Bleeding: (0.21%/year)^{1,3,4}

Drug Interactions^{1,2,3,4}:

Anticoagulants: Apixaban may enhance the effect of other anticoagulants. This combination should be avoided.^{2,3}

Antiplatelet Agents: Apixaban may enhance the anticoagulant effect of Antiplatelet Agents. Therapy should be monitored when administered concurrently.²

Carbamazepine: Concomitant administration results in decreased exposure to apixaban and an increased risk of stroke. This combination should be avoided.³

Clarithromycin: Concomitant administration results in increased exposure to apixaban and an increased risk of bleeding.³ Reduce the dose of apixaban to 2.5mg when administered concurrently with clarithromycin.³ If the patient is already receiving a reduced dose of 2.5mg, this combination should be avoided.³

Collagenase (Systemic): Apixaban may increase the risk of injection site bruising and/or bleeding associated with Collagenase (Systemic). Therapy should be monitored when administered concurrently.²

CYP3A4 Inducers (Strong): May decrease the serum concentration of apixaban. This combination should be avoided.^{1,2,3}

CYP3A4 Inhibitors (Strong): May increase the serum concentration of apixaban. This combination should be avoided.^{1,2,3}

Deferasirox: Apixaban may increase the risk of gastrointestinal ulceration/irritation or gastrointestinal bleeding associated with deferasirox. Therapy should be monitored when administered concurrently.²

Grapefruit: May increase the levels/effects of apixaban. Use with caution.²

Herbs (Anticoagulant/Antiplatelet Properties): May increase the risk of bleeding associated with apixaban. Consider modifying therapy.²

Ibritumomab: Concomitant administration may lead to an increased risk of bleeding. Therapy should be monitored when administered concurrently.²

Itraconazole: Concomitant administration results in increased exposure to apixaban and an increased risk of bleeding.³ Reduce the dose of apixaban to 2.5mg when administered concurrently with clarithromycin.³ If the patient is already receiving a reduced dose of 2.5mg, this combination should be avoided.³

Ketoconazole: Concomitant administration results in increased exposure to apixaban and an increased risk of bleeding.³ Reduce the dose of apixaban to 2.5mg when administered concurrently with clarithromycin.³ If the patient is already receiving a reduced dose of 2.5mg, this combination should be avoided.³

Nonsteroidal Anti-Inflammatory Drugs: Concomitant administration may increase the risk for bleeding. If given concurrently, patients should be educated about the signs and symptoms of bleeding and be instructed to report them immediately or go to an emergency room.³

Omacetaxine: Concomitant administration may increase the risk for bleeding-related events. Avoid concurrent use of anticoagulants with omacetaxine in patients with a platelet count < 50,000/uL.²

Omega-3 Fatty Acids: Apixaban may enhance the anticoagulant effect of omega-3 fatty acids. Therapy should be monitored when administered concurrently.²

Pentosan Polysulfate Sodium: Apixaban may enhance the anticoagulant effect of pentosan polysulfate sodium. Therapy should be monitored when administered concurrently.²

Phenytoin: Concomitant administration results in decreased exposure to apixaban and an increased risk for stroke. This combination should be avoided.³

Platelet Inhibitors: Concomitant administration may increase the risk for bleeding. If given concurrently, patients should be educated about the signs and symptoms of bleeding and be instructed to report them immediately or go to an emergency room.³

Prostacycline Analogues: Concomitant administration may lead to an increased risk of bleeding. Therapy should be monitored when administered concurrently.²

Rifampin: Concomitant administration results in decreased exposure to apixaban and an increased risk for stroke. This combination should be avoided.³

Ritonavir: Concomitant administration results in increased exposure to apixaban and an increased risk of bleeding.³ Reduce the dose of apixaban to 2.5mg when administered concurrently with clarithromycin.³ If the patient is already receiving a reduced dose of 2.5mg, this combination should be avoided.³

Selective Serotonin Reuptake Inhibitors: Concomitant administration may increase the risk for bleeding. If given concurrently, patients should be educated about the signs and symptoms of bleeding and be instructed to report them immediately or go to an emergency room.³

Serotonin Norepinephrine Reuptake Inhibitors: Concomitant administration may increase the risk for bleeding. If given concurrently, patients should be educated about the signs and symptoms of bleeding and be instructed to report them immediately or go to an emergency room.³

St. John's Wort: Concomitant administration results in decreased exposure to apixaban and an increased risk of stroke. This combination should be avoided.^{2,3}

Thrombolytic Agents: Concomitant administration may increase the risk for bleeding. If given concurrently, patients should be educated about the signs and symptoms of bleeding and be instructed to report them immediately or go to an emergency room.^{2,3}

Tipranavir: Concomitant administration may lead to an increased risk of bleeding. Therapy should be monitored when administered concurrently.²

Tositumomab and Iodine I 131 Tositumomab: Concomitant administration may increase the risk for bleeding-related events. Therapy should be monitored when administered concurrently.²

Vitamin E: Concomitant administration may lead to an increased risk of bleeding. Therapy should be monitored when administered concurrently.²

Dosing/Administration^{1,2,3,4}:

Adult Dosing: For most patients the dose is 5mg by mouth twice daily.^{1,2,3,4} If the patient has two of the following characteristics: age \geq 80 years; body weight \leq 60kg; or serum creatinine \geq 1.5mg/dL, then the dose should be reduced to 2.5mg by mouth twice daily.^{1,2,3,4}

Pediatric Dosing: Safety and efficacy in pediatric patients under 18 years old has not been established.^{1,3,4}

Geriatric Dosing: \geq 80years with 1 of the following: body weight \leq 60kg or serum creatinine \geq 1.5mg/dL, reduce dose to 2.5mg by mouth twice daily.^{1,2,3,4}

Renal Dosing: Serum creatinine \geq 1.5mg/dL with 1 of the following: age \geq 80 years or body weight \leq 60kg, reduce dose to 2.5mg by mouth twice daily.^{1,2,3,4} The American Heart Association/American Stroke Association recommends avoiding use in patients with a creatinine clearance $<$ 25mLs/min.²

Hemodialysis: Apixaban is not expected to be removed by dialysis due to high protein binding.³

Hepatic Dosing:

- Mild hepatic impairment (Child-Pugh Class A): No dosage adjustment necessary.^{1,2,3,4}
- Moderate hepatic impairment (Child-Pugh Class B): Limited clinical experience; no dosage adjustment available.^{1,2,3,4}
- Severe hepatic impairment (Child-Pugh Class C): Use is not recommended.^{1,2,3,4}

Use in special circumstances^{1,2,3,4}:

Pregnancy: Risk Category B.^{1,2,3,4} There are no adequate well-controlled studies of apixaban in pregnant women.^{1,2,3,4} Apixaban should only be used during pregnancy if the potential benefit outweighs the risks.^{1,2,3,4}

Breast-feeding: It is unknown whether apixaban or its metabolites are excreted into breast milk.^{1,2,3,4} Apixaban is not recommended for use in breast-feeding women.^{1,2,3,4}

Overdosage: There is no specific antidote to apixaban.^{1,4} Administration of activated charcoal at 2 and 6 hours after ingestion may be useful in the management of apixaban overdose or accidental ingestion by leading to a more rapid fall in apixaban blood levels.¹

Switching from warfarin to apixaban: Discontinue warfarin and start apixaban once the INR is below 2.^{1,3,4}

Switching from apixaban to warfarin: If continuous anticoagulation is necessary, discontinue apixaban and start both a parenteral anticoagulant and warfarin at the time the next apixaban dose would have been administered.^{1,3,4} Discontinue the parenteral anticoagulant once the INR is therapeutic.^{1,3,4} Apixaban affects the INR, therefore coadministration with warfarin will result in INR measurements that may not be useful for determining the appropriate dose of warfarin.^{1,3,4}

Switching between apixaban and other anticoagulants: Discontinue the current agent and initiate the preferred agent at the time the next dose would have been administered.^{1,3,4}

Conclusion: Apixaban is an effective first line therapy for stroke prophylaxis and systemic embolism prophylaxis in patients with non-valvular atrial fibrillation. Apixaban does not require monitoring of INR. Side effects associated with the drug appear to be minimal with the most significant adverse effect being bleeding, which is comparable to bleeding rates seen with warfarin and other anticoagulants. An important consideration with apixaban therapy is that there is currently not a reversal agent available for patients with significant bleeding due to apixaban therapy or patients requiring emergency surgery. Additionally apixaban like warfarin is associated with numerous drug interactions. It is unclear if there is a cost benefit for apixaban compared to warfarin when considering the emergence of point-of-care INR monitoring in recent years. Given the demonstrated superiority to warfarin with time in therapeutic range similar to what is seen with general practitioners, tolerability, and lack of INR monitoring, apixaban appears to be another clinically useful anticoagulant for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Recommended References:

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5. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-92.

6. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med.* 2011;365(23):2167-77.
7. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost.* 2007;5(12):2368-75.

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